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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,838	06/24/2003	Birthe Lykkegaard Hansen	6423.404-US	9325
23650 7590 02/06/2009 NOVO NORDISK, INC. INTELLECTUAL PROPERTY DEPARTMENT 100 COLLEGE ROAD WEST PRINCETON, NJ 08540				
EXAMINER				
HA, JULIE				
ART UNIT		PAPER NUMBER		
1654				
NOTIFICATION DATE		DELIVERY MODE		
02/06/2009		ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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# Office Action Summary

**Application No.**

10/602,838

**Applicant(s)**

HANSEN ET AL.

**Examiner**

JULIE HA

**Art Unit**

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 29 October 2008.  
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4, 6, 7, 11, 14-19, 21-26 and 29-31 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 1-4, 6, 7, 11, 14-19, 21-26 and 29-31 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.  
10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☒ All b) ☐ Some \* c) ☐ None of:  
1. ☒ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)  
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 1/31/2006 and 11/18/2008  
4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date: \_\_\_\_\_  
5) ☐ Notice of Informal Patent Application  
6) ☐ Other: \_\_\_\_\_

#### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 29, 2008 has been entered. In the Request for Continued Examiner (RCE), Applicant indicated that remarks/response and amendments were previously submitted (8/5/2008). Claims 10 and 12-13 have been cancelled. Claims 1-4, 6-7, 11, 14-19, 21-26 and 29-31 are pending in this application and examined on the merits in this office action.

#### ***Withdrawn Rejection***

2. Claims 1, 7, 14-15, 17-19, and 24 on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 1-7, 11, 12 and 16-19 of copending application No. 10/602,340 is hereby withdrawn in view of copending application being abandoned.

***Maintained Rejection***

**35 U.S.C. 103**

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purpose of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. *Joy Technologies Inc. V. Quigg*, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held in accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. *In re Hoeschele*, 160 USPQ 809, 811

(CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

6. Claims 1-4, 6-7, 11, 14-19, 21-26 and 29-31 are rejected under 35 U.S.C. 102(a) as being unpatentable over The Medicine Catalogue (Laegemiddel Kataloget), of record, in view of Pingel et al (US Patent No. 6,903,609) and Johannessen et al (WO 01/82943).

7. The Medicine Catalogue discloses a composition with recombinant coagulation factor VIIa, with 1.5 mg calcium chloride, 1.3 mg glycylglycine, 30 mg mannitol, 3.0 mg sodium chloride, and 0.1 mg polysorbate 80 per ml, wherein the composition has a pH of 5.4 to 6.0 (see Dispensed in the form on). This means that 13.51 mM of  $\text{CaCl}_2$  is in the formulation per 1 ml of solution. For sodium chloride (MW 59 g/ml) and using 3 mg and dissolving 1 ml of solution, this yields 50 mM of NaCl concentration. The Medicine Catalogue further teaches that factor VII polypeptide concentration is 1.2, 2.4 or 4.8 mg per ml of solution. When the injection fluid is prepared, this means that 0.6 mg/ml (for 1.2 mg/2ml), 1.2 mg/ml (for 2.4 mg/2 ml), 2.4 mg/ml (for 4.8 mg/2 ml) etc will be prepared. This reads on claim 29. Furthermore, the reference teaches that the preparations are dissolved in varying amounts of sterile water, and that they are administered by bolus injection (see suggest dosage), Meeting the limitation of claims 30-31. Additionally, since different amounts of sterile water are used to reconstitute the composition while the mass of the excipients does not change, the concentrations of the excipients will be commensurate with instant claims. For example, 30 mg of mannitol (MW 182.17 g/mol) used in The Medicine Catalogue, which meets the limitation of claim

11, is found to be 82 mM for 2 ml, 41 mM for 4 ml and 21 mM for 8 ml for sterile water. It is noted that claims 1-4, 6-7, 11, 14-19, 21-26 and 29-31 have been rejected over the prior art, even though the reference does not disclose exact pH range and exact amount (range) as claimed. However, the claims utilize the term "about" when discussing the pH and the amount. The term "about" allows for some tolerance in the ranges disclosed. In In re Ayers, the Federal Circuit held that "at least about 10%" was anticipated by a reference that disclosed "about 8%" because the term "about" allowed for some tolerance. In re Ayers, 154 F.2d 182, 185 (Fed. Cir. 1946). Similarly, in Johnson and Johnson v. W.L. Gore & Associates, Inc., the Court allowed for "about 1.2" to inclusive of 1.0. See Johnson and Johnson v. W.L. Gore & Associates, Inc., 436 F. Supp. 704, 728-729 (Fed. Cir. 1977). Although about has never been confined to specific percentage of variability, the Johnson and Johnson decision at least implies that 16% variability is permissible when "about" is used ( $1.0/1/2 = \sim 16.6\%$  variability). Thus the term "about" implicitly discloses some variability even though the specification may not literally cite this variability. Therefore, The Medicine Catalogue meets the limitations of claims 1-4, 6-7, 11, 14-19, 21-16 and 29-31. The difference between the reference and the instant claims is that the reference does not teach calcium salt in the concentration of at least 200 mM.

8. Pingel teaches a pharmaceutical composition comprising factor VIIa polypeptide and may contain pharmaceutically acceptable auxiliary substance or adjuvants, including without limitation, pH adjusting and buffering agents and/or tonicity adjusting agents, such as, for example, sodium acetate, sodium lactate, sodium chloride,

potassium chloride, calcium chloride, etc (see column 13, lines 54-55 and column 14, lines 9-14). Pingel teaches different calcium chloride, sodium chloride, glycylglycine buffer, mannitol and polysorbate 80 concentrations (see column 16, lines 26-39).

9. Johannessen et al disclose factor VIIa for the manufacture of a medicament for treatment of condition affectable by Factor VIIa, medicament being for subcutaneous, intra-muscular or intradermal administration...shows a prolonged biological half-life (see abstract). Calcium or other divalent metal ions, is necessary for the maintenance of the FVIIa activity...calcium chloride...in an amount of more than 0.15 mg/ml (see p. 19, lines 25-28). Additionally, the reference discloses that the medicament may also comprise salt in order to give an isotonic solution, e.g. NaCl, KCl...in an amount of more than 1.0 mg/ml (see p. 9, lines 22-24). The reference further discloses that preservatives such as benzyl alcohol, phenol, sorbic acid, parabens, and chlorocresol may be added (see p. 10, lines 1-14). Please note that the instant specification discloses that factor VII polypeptide include factor VIIa (see paragraph [0017]) and that factor VII polypeptide is human factor VIIa, recombinant human VIIa, a factor VII-related polypeptide, factor VII sequence variant (see paragraph [0043]).

10. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of The Medicine Catalogue, Johannessen and Pingel to produce a liquid, aqueous composition comprising factor VII polypeptide, since the Medicine Catalogue, Johannessen and Pingel teach the formulation of Factor VII. Therefore, one of ordinary skilled in the art would have been motivated to optimize the  $\text{CaCl}_2$  concentration, since Johannessen indicates that  $\text{CaCl}_2$  maintains the FVIIa activity, and

is required in an amount more than 0.15 mg/ml. The MPEP states the following:

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 (“*The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.*”); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Therefore, there is a reasonable expectation of success, since having a CaCl<sub>2</sub> concentration in an amount



more than 0.15 mg/ml maintains FVIIa activity, optimizing the concentration would stabilize FVIIa activity. Since artisans are always trying to optimize the peptide stability and maintain peptide activity, by optimizing the  $\text{CaCl}_2$  concentration in an amount more than 0.15 mg/ml, one would at least expect a more stable liquid formulation.

### ***Response to Applicant's Arguments***

11. Applicant argues that the "present invention is directed to a composition that comprises a calcium salt in a concentration of at least 200 mM, such that the composition is hypertonic." Applicant argues that "In contrast, neither The Medicine Catalogue or Johannessen teach or suggest a composition comprising anywhere near the amount of 29.4 mg/ml of  $\text{CaCl}_2$ ...the present invention is based on the discovery that such hypertonic compositions dramatically results in a decreased formation of heavy chain fragments during storage for as long as six months...the present invention is not based upon the optimization of known ranges within the art by routine experimentation, but instead the discovery of a critical aspect of maintaining the stability of such Factor VII formulations."

12. Applicant's arguments have been fully considered but have not been found persuasive. The Medicine Catalogue, Pingel et al and Johannessen et al teach that calcium or other divalent metal ions are necessary for the maintenance of the FVIIa activity. Since the calcium or other divalent metal ions are necessary for the maintenance of the FVIIa activity, and is required in an amount more than 0.15 mg/ml  $\text{CaCl}_2$ , and The Medicine Catalogue utilized 1.5 mg of  $\text{CaCl}_2$ , it would have been

obvious to one of ordinary skill in the art to optimize the amount or the concentration of the calcium chloride to optimize the activity of the FVIIa. All references teach utilizing different concentrations of  $\text{CaCl}_2$  in the formulation. Furthermore, Johannessen does not give an upper limit for the  $\text{CaCl}_2$  concentration, therefore, one of ordinary skill in the art would have been motivated to try the highest concentration of  $\text{CaCl}_2$  (saturation point) and work down from that point to optimize the concentration. One of ordinary skill in the art would be motivated to optimize the concentration of the divalent metal, since the normal desire of an artisan is to optimize or improve upon what is generally known through routine optimization. There is a reasonable expectation of success, since The Medicine Catalogue, Pingel and Johannessen references teach that  $\text{CaCl}_2$  maintained the activity of FVIIa, thus optimizing the  $\text{CaCl}_2$  concentration would at least optimize the FVIIa activity. Therefore, optimization of  $\text{CaCl}_2$  is deemed merely a matter of judicious selection and routine optimization that is well within the purview of skilled artisan.

13. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., decreased formation of heavy chain fragment during storage for as long as six months) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

***Obviousness Double Patenting***

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-4, 6-7, 11, 14-19, 21-26 and 29-31 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,833,352 in view of US Patent No. 6,310,183 (as filed with IDS).

Although the conflicting claims are not identical, they are not patentably distinct from each other because if one practiced the claimed invention of instant application, one would necessarily achieve the claimed invention of US Patent No. '352 and vice versa.

16. Instant claims are drawn to a liquid, aqueous composition comprising a factor VII polypeptide, an agent suitable for keeping pH in the range of from about 5.5 to about 7.0, a calcium salt in a concentration of at least 200 mM, wherein said composition

retains at least 50% of its initial biological activity upon storage of said aqueous composition for 6 months at 2-8C.

17. Claims of US Patent No. '352 are drawn to a method for treatment of a disease affectable by Factor VIIa, said method comprising administering subcutaneously to a mammal in need thereof an effective amount for treating said disease of a composition comprising modified FVIIa. Since the US Patent teaches a method of treatment comprising the FVIIa composition, the patent comprises the composition comprising FVII polypeptide. The difference between the reference and the instant claims is that the reference does not teach pH and calcium salts.

18. However, US Patent No. 6,310,183 teaches a method for treatment of a disease affectable by FVIIa, said method comprising administering subcutaneously to a mammal in need thereof an effective amount for treating said disease of a composition comprising FVIIa, and a method for prolonging the biological half-life of FVIIa being administered to a mammal. The reference further teaches a composition consisting of rFVIIa, sodium chloride, glycinglycine, polysorbate 80, calcium chloride, water, mannitol at pH 5.5 (see for example, column 7, lines 45-55). The reference further teaches methionine as an antioxidant (see column 7, lines 23-26).

19. Therefore, it would have been obvious to one of ordinary in the art to combine the teachings of US Patent No. '352 and '183 to prolong the biological activity of the composition comprising FVII polypeptide for a method of treating a factor-VII related syndrome. Therefore if one of ordinary skill in the art practiced the claimed invention of

the instant application, one would necessarily achieve the claimed invention of US Patent No. 6,833,352.

20. Claims 1-4, 6-7, 11, 14-19 and 22-31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-12, 17, 20-22, 26 and 27-28 of copending Application No. 11/473,387 (US 2007/0049523 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because if one of ordinary skill in the art practiced the claimed invention of instant claims, one would necessarily achieve the claimed invention of 11/473,387 and vice versa.

21. The instant claims are drawn to a liquid, aqueous composition comprising a factor VII polypeptide, an agent suitable for keeping pH in the range of from about 5.5 to about 7.0, a calcium salt in a concentration of at least 200 mM.

22. The claims of copending application are drawn to a liquid, aqueous composition comprising a modified factor VII polypeptide, an agent suitable for keeping pH in the range of from about 4.0 to about 8.0, an antioxidant, an agent selected from a calcium salt and a method for preparing a liquid, aqueous composition. The dependent claims recite, L- or D-methionine, mannitol, polysorbate, glycylglycine, 1 mM to 500 mM (10-250 mM) tonicity modifying agent (calcium chloride) and so on (see claims 1-4, 6-12, 17, 20-22, 26 and 27-28).

23. Therefore, if one of ordinary skill in the art practiced the claimed invention of instant claims, one would necessarily achieve the claims of copending application and vice versa.

This is a provisional obviousness-type double patenting rejection.

### ***Conclusion***

24. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. H./  
Examiner, Art Unit 1654

/Cecilia Tsang/  
Supervisory Patent Examiner  
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